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Reply to Künzli and Tager Regarding Causality in PM_{2.5} Cohort Studies

Künzli and Tager suggest that my critique (1) of PM_{2.5} and mortality in long-term prospective cohort studies is full of inaccuracies and misconceptions about ecological studies. As in most arguments, there are issues on which there is agreement, others where there is disagreement, and some areas of misunderstanding. I will briefly discuss those relevant issues on which we disagree. I believe that the cohort studies are accurately described, that the ambient PM_{2.5} concentrations are inadequate surrogates for individual-level exposure, and that these studies are subject to some biases and inaccuracies common to true ecological studies. In my paper (1), I suggested that risk estimates based on ambient concentration levels should be tested for plausibility using other studies with both individual-level exposure and response data, and I applied such a test. I presented evidence that short-term exposures in time-series studies are not coherent with long-term health effects and that long-term morbidity

findings may not be coherent with mortality. I suggested that the Six Cities results might be confounded, using between-city differences in lung function as one example.

I did not present the air pollution studies as being truly ecological. In my paper (1), I described the cohort studies as “a mixed design incorporating both individual-level data...and group-level data on ambient air pollution concentrations.” More precise terms such as semiecological, or hybrid, or semi-individual may be helpful. In my opinion, a lack of consideration for the limitations inherent in ecological exposure variables has led to significant errors in interpretation.

Künzli and Tager appear to suggest that the pollution exposure variable is not ecological because it is derived from measurement (i.e., it is a “crude, average ambient concentration”). It is true that Brenner et al. (2) state that in “ecologic studies, the exposure status of groups is often defined by the proportion of individuals exposed.” Künzli and Tager apparently missed the word “often” or interpreted it as “always.” Brenner et al. (2) go on to indicate that exposure characterized by a single common measure such as “area air pollution” is an ecologic exposure variable.

We seem to agree that there are errors in using ambient concentrations as surrogate measures for individual exposure, that these errors influence the risk estimates, and that these are critical questions. We appear to disagree on how great is the effect, how to estimate the effect of these errors, and whether I have addressed the issues at all.

I discussed exposure misclassification, and I concluded that since all inhabitants in a given city are assumed to have the same exposure to PM_{2.5}, there are large errors for many members of the cohorts (1). Therefore, the group-level exposure variable is not an adequate surrogate for personal exposure, and as a result, the risk estimates may be biased to an unknown extent and direction. The magnitude and direction of this misclassification bias cannot be easily estimated because it has been repeatedly shown that even apparently nondifferential misclassification can cause spurious results in either direction (3-8). In fact, when the true relative risk is near 1.00 (as is the case for PM), an appreciable percentage of studies will overestimate the risk (9). When the true relative risk is exactly 1.00, the misclassified risk estimates are evenly distributed above and below 1.00 (8). While exposure misclassification may be reduced by the use of such individual-level data as time-activity patterns or work exposure [as in the studies of the Seventh Day Adventists (SDAs) (10)], the potential for error still remains.

It is true that semiecological studies gather some covariate estimates for individuals, providing some control of confounding. However, considerable residual confounding can still occur if important confounders are missed or crudely measured (5,11-15). Furthermore, for individual-level confounding to be effectively removed, the nature of the association between the exposure and the confounder should be well specified, which is not possible when exposure information for individuals is lacking.

Some questions regarding the inaccuracies associated with the risk estimates from these studies may be addressed in ways suggested by Künzli and Tager. I go beyond these suggestions to propose that the ultimate validity of the risk estimates in these studies is basically unknown. The risk estimates must be verified or refuted by a different study design utilizing individual-level data for exposure, outcome, and confounding variables (1).

This process of verification or refutation is an essential part of the scientific method in general and epidemiology in particular (16). A primary focus of my critique was to verify and refute the mortality risk estimates from the Six Cities (17) and American Cancer Society (ACS) (18) cohorts. This validity check was done by comparing the cardiopulmonary mortality risk estimates for ambient PM_{2.5} with the risk estimates for tobacco smoke in these same studies. The rationale for this comparison was that the individual-level exposure to tobacco smoke PM was well characterized, that the associations between tobacco smoke and cardiopulmonary mortality are widely accepted as causal, and that tobacco smoke PM is a reasonable surrogate for ambient PM_{2.5}. The comparability of the ambient PM_{2.5} and tobacco smoke risk estimates would be a validity check and would provide some estimate of the degree and direction of bias if the results were not comparable. For a given PM_{2.5} concentration, the risk estimates from ambient exposures were orders of magnitude greater than those from tobacco exposures. Therefore, I concluded that the ambient PM_{2.5} risk estimates in the Six Cities (17) and ACS (18) cohort studies are not biologically plausible (1).

I and others (17,19) disagree with Künzli and Tager that short-term mortality in time-series studies is relevant to the coherence argument because the time-series studies look at short-term exposures rather than chronic or lifetime exposures. Also, the health outcomes in time-series studies are usually thought to be in the elderly and other susceptible people (20) rather than in the total population.

It is unclear whether the SDA long-term morbidity results (10) are coherent with mortality results. Among individuals who were symptom-free at the start of the study, there was an association between increased symptoms and PM. These risk estimates were 40-fold greater than those estimated for smoking. There were no analyses presented for those individuals who had symptoms at the start of the study, but became symptom-free at the end of the study. This analysis is just as important as the analysis of incidence of new symptoms. If both showed an association with PM, the results would not be internally coherent (1).

I presented evidence showing why reduced lung function could be a confounder in these studies and that it meets the criteria for confounding. First, reduced lung function must be a risk factor for increased mortality (1). Second, reduced lung function must be correlated with between-city variations in PM_{2.5}, although the relationship shown in Figure 3 (1) could only be tested with the ecologically based exposure measures used in that study. Third, reduced lung function should not be on the same causal pathway as PM_{2.5} for mortality; the point of the example shown in Figure 4 (1) was to suggest that important differences occur in the distribution of risk factors between cities, with lung function being one of many possible risk factors. I do not believe that adjustment for a few individual-level risk factors has adequately addressed the complex overall potential for confounding in these studies. We all realize that we can never make all groups completely comparable, but between-city differences in PM_{2.5} concentrations are so small and relative risks so low that these studies are particularly susceptible to even slightly confounded results.

I believe this paper (1) and the questions raised by Künzli and Tager are in line with the scientific process of verification and refutation. They have led to further discussion that will hopefully lead to additional testing. However, it is disappointing that Künzli and Tager chose to question the integrity of the author's motivation based on affiliation. Judgment on whether or not my critique clouds the complex issues around PM_{2.5} and mortality should be determined not by my affiliation but solely on the scientific merits of the argument.

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Methylmercury Neurotoxicity Independent of PCB Exposure

A prospective study of methylmercury neurotoxicity in a Faroese birth cohort (1) has been scrutinized at a workshop recently summarized in *EHP* (2). The meeting was convened by the NIEHS on behalf of the White House Office of Science and Technology Policy. One of the main issues considered by the expert panels was whether concomitant prenatal exposure to polychlorinated biphenyls (PCBs) affected

the neurobehavioral response variables assessed at 7 years of age. In a previously published paper (1), we showed that adjustment for the cord PCB concentration barely changed the regression coefficients for the cord-blood mercury concentration as a predictor of neurobehavioral deficits. In response to questions raised at the workshop, we have now conducted some additional analyses to explore this issue.

On the basis of the 436 cord PCB analyses completed (1), children with complete data were divided into tertile PCB exposure groups. The main source of increased PCB exposure in the Faroe Islands is whale blubber, but almost half of Faroese mothers are known not to eat this food item (3). The lowest tertile is therefore thought to correspond to a control group with a background exposure to PCB. Based on psychometric properties, one outcome variable was selected to reflect each of five different domains of brain function, i.e., motor function, attention, visuospatial function, language, and memory (1). A regression equation with a uniform series of confounder variables (1) was then fitted to the data for each of the three subgroups.

Table 1 shows the regression coefficients for the logarithmic transformation of the cord-blood mercury concentration, i.e., the change in the outcome variable associated with a 10-fold increase in methylmercury exposure. The hypothesis of no difference between the regression coefficients was then tested, and in all cases resulted in an acceptance of the hypothesis, with *p*-values of 0.16-0.94. Accordingly, the effect of mercury exposure can be explained by three parallel lines. The hypothesis of no PCB effect resulted in *p*-values between 0.07 and 0.73, thus suggesting no difference in the intercept between the three lines. Thus, given the acceptance of both null hypotheses, the effect of mercury exposure on each of the five neurobehavioral outcome variables can be explained by a single line. All mercury regression coefficients for the control group suggest a deficit at increasing concentrations similar to the one for the overall material (1). Also, when compared to the two other tertile groups, the mercury effect in the control group was the greatest for three of five outcome variables.

However, some information may be lost, as the PCB exposure variable in this analysis was reduced to tertile classes only. Thus, the possible effect modification by PCB exposure was investigated in regression analyses, which in addition to the confounders, also included the mercury and PCB exposure variables as well as a product term between the two exposure biomarkers. The *p*-value for no effect modification was between 0.21